

WHAT IS CLAIMED IS:

1. An isolated or recombinant nucleic acid comprising a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO:1, wherein the nucleic acid encodes at least one polypeptide having an NFkB activating activity.
2. The isolated or recombinant nucleic acid of claim 1, wherein the NFkB activating activity comprises mediating the assembly of CARD-containing proteins into apoptosis signaling complexes.
3. The isolated or recombinant nucleic acid of claim 1, wherein the NFkB activating activity comprises mediating the assembly of CARD-containing proteins into NF-kappaB signaling complexes.
4. The isolated or recombinant nucleic acid of claim 1, wherein the NFkB activating activity comprises being a molecular scaffold for the assembly of a multi-molecular complex.
5. The isolated or recombinant nucleic acid of claim 1, wherein the NFkB activating activity comprises recruitment of a signaling protein into a multi-molecular complex.
6. The isolated or recombinant nucleic acid of claim 5, wherein the signaling protein comprises a Bcl10, a calcineurin, a PKCtheta, a PKCbeta, an IKKalpha, an IKKbeta, an IKKgamma, an IkappaB (IκB), a vav, a MALT1, an AKT/PKB, an MEKK1, an MEKK2, an MLK3, a Cot/Tpl2 or an NIK.
7. An isolated or recombinant nucleic acid comprising a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO:3.
8. An isolated or recombinant nucleic acid comprising a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO:4.

9. A first nucleic acid molecule for identifying a second nucleic acid molecule, wherein the second nucleic acid molecule encodes a polypeptide with an NFkB activating activity, wherein the first nucleic acid molecule comprises at least 10 consecutive bases of a sequence as set forth in SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:4, and further wherein the first nucleic acid molecule identifies the second nucleic acid molecule by binding or hybridization.
10. An expression cassette comprising a nucleic acid comprising a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:4.
11. A vector comprising a nucleic acid comprising a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:4.
12. A transformed cell comprising a vector according to claim 11.
13. The transformed cell of claim 14, wherein the cell is a bacterial cell, a mammalian cell, a fungal cell, a yeast cell, an insect cell or a plant cell.
14. A cloning vehicle comprising a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:4.
15. The cloning vehicle of claim 12, wherein the nucleic acid sequence is contained within a recombinant virus, a plasmid, a phage, a phagemid, a cosmid, a fosmid, a bacteriophage or an artificial chromosome.
16. An antisense oligonucleotide comprising a nucleic acid sequence complementary to or capable of hybridizing under stringent conditions to a nucleic acid sequence with at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:4.
17. A method of inhibiting an NFkB activity in a cell comprising administering to the cell or expressing in the cell an antisense oligonucleotide according to claim 16.

18. A double stranded RNA oligonucleotide comprising a nucleic acid sequence complementary to or capable of hybridizing under stringent conditions to a nucleic acid sequence with at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:4.

19. A method of inducing the degradation by RNA interference of a message in a cell comprising administering to the cell or expressing in the cell a double stranded RNA molecule, or a molecule predicted to fold into a double stranded form, or two complementary RNA molecules that are capable of hybridizing to form a double stranded RNA molecule, wherein the double stranded RNA molecule comprises a nucleic acid sequence complementary to or capable of hybridizing under stringent conditions to a nucleic acid sequence at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:4.

20. An isolated or recombinant polypeptide comprising (i) an amino acid sequence having at least 95% sequence identity to SEQ ID NO:2; or (ii) an amino acid sequence encoded by a nucleic acid comprising a sequence having at least 90% sequence identity to SEQ ID NO:1; wherein the polypeptide has an NFkB activating activity.

21. The isolated or recombinant polypeptide of claim 20, wherein the NFkB activating activity comprises mediating the assembly of CARD-containing proteins into apoptosis signaling complexes.

22. The isolated or recombinant polypeptide of claim 20, wherein the NFkB activating activity comprises mediating the assembly of CARD-containing proteins into NF-kappaB signaling complexes.

23. The isolated or recombinant polypeptide of claim 20, wherein the NFkB activating activity comprises being a molecular scaffold for the assembly of a multi-molecular complex.

24. The isolated or recombinant polypeptide of claim 20, wherein the NFkB activating activity comprises recruitment of a signaling protein into a multi-molecular complex.

25. The isolated or recombinant polypeptide of claim 24, wherein the signaling protein comprises a Bcl10, a calcineurin, a PKCtheta, a PKCbeta, an IKKalpha, an IKKbeta, an IKKgamma, an IkappaB (IκB), a vav, a MALT1, an AKT/PKB, an MEKK1, an MEKK2, an MLK3, a Cot/Tpl2 or an NIK.

26. An isolated or recombinant antibody that specifically binds to a polypeptide according to claim 20.

27. A hybridoma comprising an antibody according to claim 26.

28. A method for identifying a polypeptide having an NFκB activating activity, said method comprising:

contacting a polypeptide according to claim 20, or a fragment thereof, with two or more molecules that multimerize or specifically associate in the presence of an NFκB activating polypeptide; and

detecting multimerization or specific association of the molecules;

wherein multimerization or specific association of the molecules identifies the polypeptide as having an NFκB activating activity.

29. A method for identifying a polypeptide having an NFκB activating activity, said method comprising:

contacting a polypeptide according to claim 20, or a fragment thereof, with a construct comprising an NFκB-responsive promoter operably linked to a reporter gene; and

detecting the amount of reporter gene product produced;

wherein an increase in the amount of reporter gene product identifies the polypeptide as having an NFκB activating activity.

30. A method of determining whether a test compound specifically binds to a polypeptide according to claim 20, or a fragment thereof, said method comprising:

contacting the polypeptide or fragment thereof with the test compound; and

determining whether the test compound specifically binds to the polypeptide, thereby determining that the test compound specifically binds to the polypeptide.

31. A method for identifying a modulator of an NFkB activating activity, said method comprising:

contacting a polypeptide according to claim 20, or a fragment thereof, with a test compound; and

measuring an activity of the NFkB activating polypeptide;

wherein a change in NFkB activating activity measured in the presence of the test compound as compared to the NFkB activating activity in the absence of the test compound provides a determination that the test compound modulates an activity of the NFkB activating polypeptide.

32. The method of claim 31, further comprising providing two or more molecules that multimerize or specifically associate in the presence of an NFkB activating polypeptide, wherein the NFkB activating activity is measured by detecting an increase or decrease in the amount of multimerization or specific association of the molecules.

33. A method for identifying a polypeptide able to upregulate the activity of an NFkB activity, said method comprising:

contacting a polypeptide according to claim 20, or a fragment thereof, with a reporter gene with activity determined by the activation state of an NFkB; and

detecting an increase in reporter gene activity;

wherein an increase in the amount of reporter gene activity identifies a polypeptide able to upregulate the activity of NFkB.

34. A method for determining a functional fragment of an NFkB activating polypeptide, said method comprising:

deleting a plurality of amino acid residues from a polypeptide according to claim 20 to create a subsequence thereof; and

testing the subsequence for an NFkB activating activity, thereby determining a functional fragment of an NFkB activating polypeptide.

35. A transgenic non-human animal comprising a heterologous nucleic acid, wherein the nucleic acid comprises a sequence having at least 90% sequence identity to SEQ ID NO:1 SEQ ID NO:3, or SEQ ID NO:4, wherein said animal exhibits a phenotype, relative to a wild-type phenotype comprising a characteristic selected from the group consisting of a dermatitis, a B cell defect, a T cell defect, and a combination of any two or more thereof.

36. The transgenic non-human animal of claim 35, wherein the animal is a mouse or a rat.

37. A cell or cell line derived from a transgenic non-human animal according to claim 35.

38. An *in vitro* method of screening for a modulator of an NFkB activating activity, said method comprising:

contacting a cell or cell line according to claim 37 with a test compound; and
detecting an increase or a decrease in the amount of an NFkB reporter gene, an NFkB transcript, an NFkB protein, or an NFkB activity; thereby identifying the test compound as a modulator of an NFkB activating activity.

39. An *in vivo* method of screening for a modulator of an NFkB activating activity, said method comprising:

contacting a transgenic non-human animal according to claim 35 with a test compound;
and

detecting an increase or a decrease in the amount of an NFkB reporter gene, an NFkB transcript, an NFkB protein, or an NFkB activity; thereby identifying the test compound as a modulator of an NFkB activating activity.

40. An *in vivo* method for screening for a modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

contacting a transgenic non-human animal according to claim 35 with a test compound;
and

detecting an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect;

wherein the increase or the decrease identifies the test compound as a modulator of the dermatitis, the B cell defect, or the T cell defect.

41. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

inserting a test gene into one or more cells of a transgenic non-human animal according to claim 35; and

detecting an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect;

wherein the increase or decrease identifies the test gene as a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

42. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

mating a first transgenic non-human animal according to claim 35 with a second non-human animal of a sex opposite of the first transgenic non-human animal, wherein the second non-human animal is selected from the group consisting of an inbred non-human animal strain, a randomly mutagenized non-human animal, a transgenic non-human animal, and a knockout non-human animal; and

selecting an offspring of the mating that exhibits an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect, thereby identifying a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

43. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

(i) mating a first transgenic non-human animal according to claim 35 with a second non-human animal of a sex opposite of the first transgenic non-human animal, wherein the second non-human animal is a randomly mutagenized non-human animal;

(ii) mating two offspring of the mating of step (i); and

(iii) identifying offspring of the mating of step (ii) that carry two mutated alleles of a nucleic acid having at least 90% identity with SEQ ID NO:1 and that exhibit an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect, thereby identifying a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

44. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

(i) mating a first transgenic non-human animal according to claim 35 with a second non-human animal of a sex opposite of the first transgenic non-human animal, wherein the second non-human animal is a randomly mutagenized non-human animal;

(ii) mating an offspring of the mating of step (i) with a transgenic non-human animal according to claim 35; and

(iii) identifying offspring of the mating of step (ii) that carry two mutated alleles of a nucleic acid having at least 90% identity with SEQ ID NO:1 and that exhibit an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect, thereby identifying a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

45. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

(i) mating a first transgenic non-human animal according to claim 35 with a second non-human animal of a sex opposite of the first transgenic non-human animal, wherein the second non-human animal is a randomly mutagenized non-human animal;

(ii) mating an offspring of the mating of step (i) with a randomly mutagenized non-human animal; and

(iii) identifying offspring of the mating of step (ii) that carry a mutated allele of a nucleic acid having at least 90% identity with SEQ ID NO:1 and that exhibit an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect, thereby identifying a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

46. A knockout non-human animal, wherein an endogenous gene sequence comprising a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO:1 or SEQ ID NO:3 is disrupted so as to produce a phenotype comprising a characteristic selected from the group consisting of a dermatitis, a B cell defect, a T cell defect, and a combination of any two or more thereof.

47. The knockout non-human animal of claim 46, wherein the animal is a mouse or a rat.

48. A cell or cell line derived from a knockout non-human animal according to claim 46.

49. An *in vivo* method for screening for a modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

contacting a knockout non-human animal according to claim 46 with a test compound;
and

detecting an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect;

wherein the increase or the decrease identifies the test compound as a modulator of the dermatitis, the B cell defect, or the T cell defect.

50. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

inserting a test gene into one or more cells of a knockout non-human animal according to claim 46; and

detecting an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect;

wherein the increase or decrease identifies the test gene as a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

51. An inbred mouse comprising a genome that is homozygous for a nucleic acid sequence encoding a polypeptide having at least 95% sequence identity to SEQ ID NO:2, wherein said polypeptide comprises a change in the amino acid sequence of SEQ ID NO:2 at amino acid residue number 298.

52. An inbred mouse according to claim 51, wherein the polypeptide comprises a sequence as set forth in SEQ ID NO:5.

53. An inbred mouse according to claim 51, wherein the mouse has a phenotype comprising a characteristic selected from the group consisting of a dermatitis, a B cell defect, and a T cell defect.

54. A cell or cell line derived from an inbred mouse according to claim 51.

55. An *in vitro* method of screening for a modulator of an NFkB activating activity, said method comprising:

contacting a cell or cell line according to claim 54 with a test compound; and
detecting an increase or a decrease in the amount of an NFkB reporter gene, an NFkB transcript, an NFkB protein, or an NFkB activity; thereby identifying the test compound as a modulator of an NFkB activating activity.

56. An *in vivo* method of screening for a modulator of an NFkB activating activity, said method comprising:

contacting an inbred mouse according to claim 51 with a test compound; and
detecting an increase or a decrease in the amount of an NFkB reporter gene, an NFkB transcript, an NFkB protein, or an NFkB activity; thereby identifying the test compound as a modulator of an NFkB activating activity.

57. An *in vivo* method for screening for a modulator of a dermatitis, a B cell defect, a T cell defect, said method comprising:

contacting an inbred mouse according to claim 51 with a test compound; and
detecting an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect;

wherein the increase or the decrease identifies the test compound as a modulator of the dermatitis, the B cell defect, or the T cell defect.

58. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

inserting a test gene into one or more cells of an inbred mouse according to claim 51; and
detecting an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect;

wherein the increase or decrease identifies the test gene as a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

59. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

mating a first inbred mouse according to claim 51 with a second mouse of a sex opposite of the first inbred mouse, wherein the second mouse is selected from the group consisting of an inbred mouse strain, a randomly mutagenized mouse, a transgenic mouse, and a knockout mouse; and

selecting an offspring of the mating that exhibits an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect, thereby identifying a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

60. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

(i) mating a first inbred mouse according to claim 51 with a second mouse of a sex opposite of the first inbred mouse, wherein the second mouse is a randomly mutagenized non-human animal;

(ii) mating two offspring of the mating of step (i); and

(iii) identifying offspring of the mating of step (ii) that carry two mutated alleles of a nucleic acid having at least 90% identity with SEQ ID NO:1 and that exhibit an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect, thereby identifying a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

61. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

- (i) mating a first inbred mouse according to claim 51 with a second mouse of a sex opposite of the first inbred mouse, wherein the second mouse is a randomly mutagenized non-human animal;
- (ii) mating an offspring of the mating of step (i) with an inbred mouse according to claim 51; and
- (iii) identifying offspring of the mating of step (ii) that carry two mutated alleles of a nucleic acid having at least 90% identity with SEQ ID NO:1 and that exhibit an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect, thereby identifying a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

62. An *in vivo* method to identify a genetic modulator of a dermatitis, a B cell defect, or a T cell defect, said method comprising:

- (i) mating a first inbred mouse according to claim 51 with a second mouse of a sex opposite of the first inbred mouse, wherein the second mouse is a randomly mutagenized mouse;
- (ii) mating an offspring of the mating of step (i) with a randomly mutagenized mouse; and
- (iii) identifying offspring of the mating of step (ii) that carry a mutated allele of a nucleic acid having at least 90% identity with SEQ ID NO:1 and that exhibit an increase or a decrease in the amount or severity of the dermatitis, the B cell defect, or the T cell defect, thereby identifying a genetic modulator of the dermatitis, the B cell defect, or the T cell defect.

63. A method for generating a toleragenic signal in a subject, said method comprising administering to the subject an amount of an antisense oligonucleotide according to claim 16 sufficient to inhibit the expression of a CARD11 polypeptide, thereby generating a T cell defect and generating a toleragenic signal in the subject.

64. A method for generating a toleragenic signal in a subject, said method comprising administering to the subject an amount of an antibody according to claim 26 sufficient to inhibit the activity of a CARD11 polypeptide, thereby generating a T cell defect and generating a toleragenic signal in the subject.

65. A method for tolerizing a subject to an antigen, said method comprising:
administering to the subject an amount of an antisense polynucleotide according to claim 16 sufficient to inhibit the expression of a CARD11 polypeptide, thereby generating a T cell defect and generating a toleragenic signal in the subject; and
administering an antigen to the subject, thereby tolerizing the subject to the antigen.

66. A method for tolerizing a subject to an antigen, said method comprising:
administering to the subject an amount of an antibody according to claim 26 sufficient to inhibit the expression of a CARD11 polypeptide, thereby generating a T cell defect and generating a toleragenic signal in the subject; and
administering an antigen to the subject, thereby tolerizing the subject to the antigen.

67. A method for tolerizing a subject to an antigen, said method comprising:
administering to the subject an amount of small molecule inhibitor to a polypeptide having an NFkB activating activity according to claim 20 sufficient to inhibit the expression of a CARD11 polypeptide, thereby generating a T cell defect and generating a toleragenic signal in the subject; and
administering an antigen to the subject, thereby tolerizing the subject to the antigen.

68. A method of treating an autoimmune disease or a lymphoma, said method comprising modulating a polypeptide having NFkB activating activity by administering a compound that binds to or modulates a polypeptide comprising (i) an amino acid sequence having at least 95% sequence identity to SEQ ID NO:2; or (ii) an amino acid sequence encoded by a nucleic acid comprising a sequence having at least 90% sequence identity to SEQ ID NO:1; wherein the polypeptide has an NFkB activating activity.